Brain Targeting Drug Delivery System

Pshtiwan Ghareeb Ali

University of sulaimany
College of Pharmacy
Pharmaceutics department

April 23, 2014

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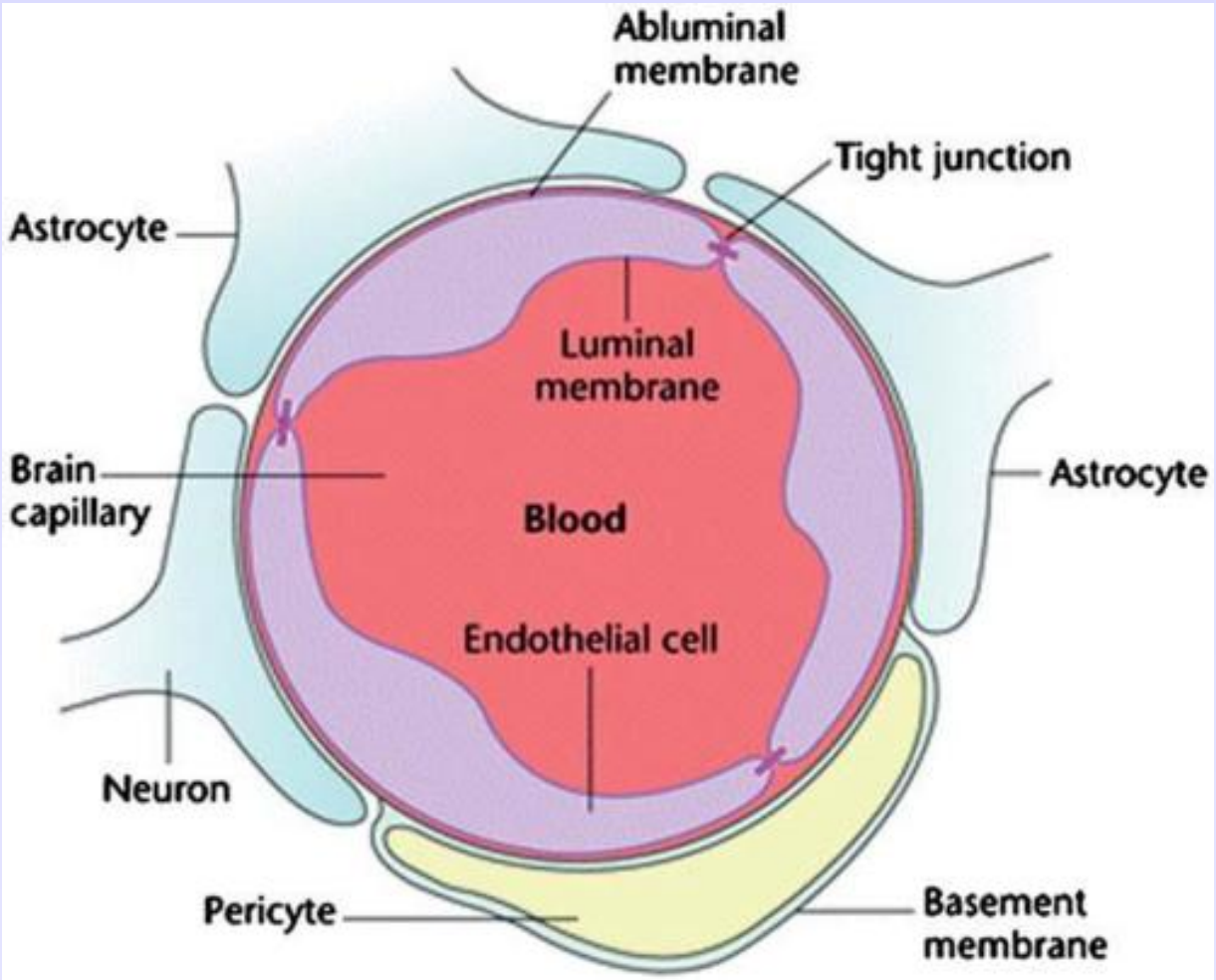
- The major component of the BBB is a monolayer of brain capillary endothelial cells
- The restriction of brain penetration arises from the presence of tight junctions between adjacent endothelial cells and the relative paucity of fenestrae and pinocytotic vesicles
- Brain endothelial cells are characterized with **tight junctions (tj)** that lock the aqueous paracellular pathways, negligible pinocytotic activity, **high efflux transport**, and **high metabolic activity**, They are in close relationship with pericytes, astrocyte foot processes, axonal endings, and microglial cells.

BBB


Abluminal membrane
Tight junction
Astrocyte
Luminal membrane
Brain capillary
Blood
Astrocyte
Endothelial cell
Neuron
Pericyte
Basement membrane

CNS therapeutics as substrates of BBB efflux transporters

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- Due to the BBB, circulating compounds can only gain access to the brain via lipid-mediated transport of small nonpolar molecules through the BBB by passive diffusion or less frequently by catalyzed transport
- Uptake can be lower than predicted for compounds which are subject to extrusion from the brain by active BBB efflux transporters.

Pharmacological group	Examples	Transporters involved
Anticancer drugs	Doxorubicin, daunorubicin, vinblastin, vincristine, paclitaxel, etoposide, topotecan	ABCB1/Pgp, ABCC transporters/MRPs, ABCG2/BCRP
Analgesics	Morphine, methadone, fentanyl	ABCB1/Pgp
HIV protease inhibitors	Amprenavir, indinavir, saquinavir	ABCB1/Pgp, ABCC transporters/MRPs
Antipsychotic agents	Olanzapine, amisulpride	ABCB1/Pgp
Antiepileptic drugs	Phenytoin, carbamazepine, oxcarbazepine, lamotrigine, phenobarbital, felbamate, valproic acid, topiramate	ABCB1/Pgp, ABCC transporters/MRPs
Antidepressants	Amitryptiline, nortryptiline, venlafaxine, paroxetine	ABCB1/Pgp

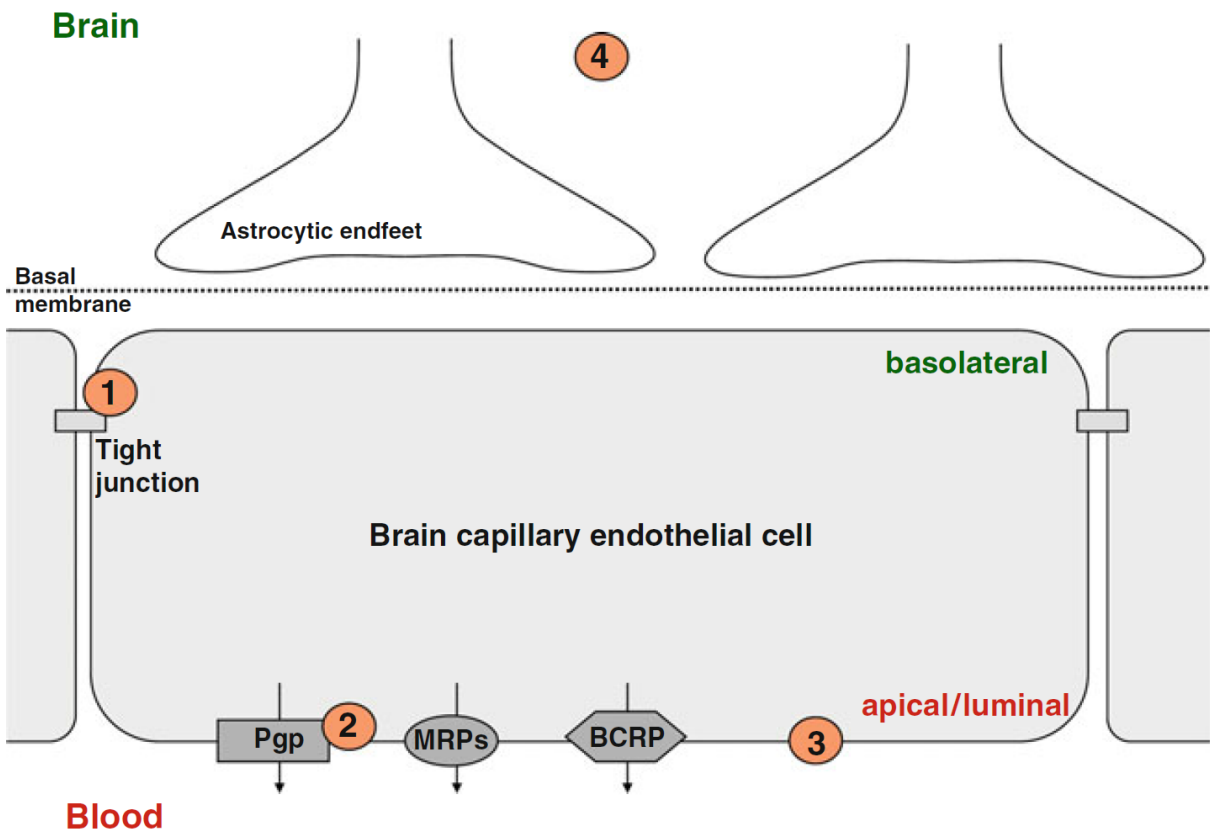
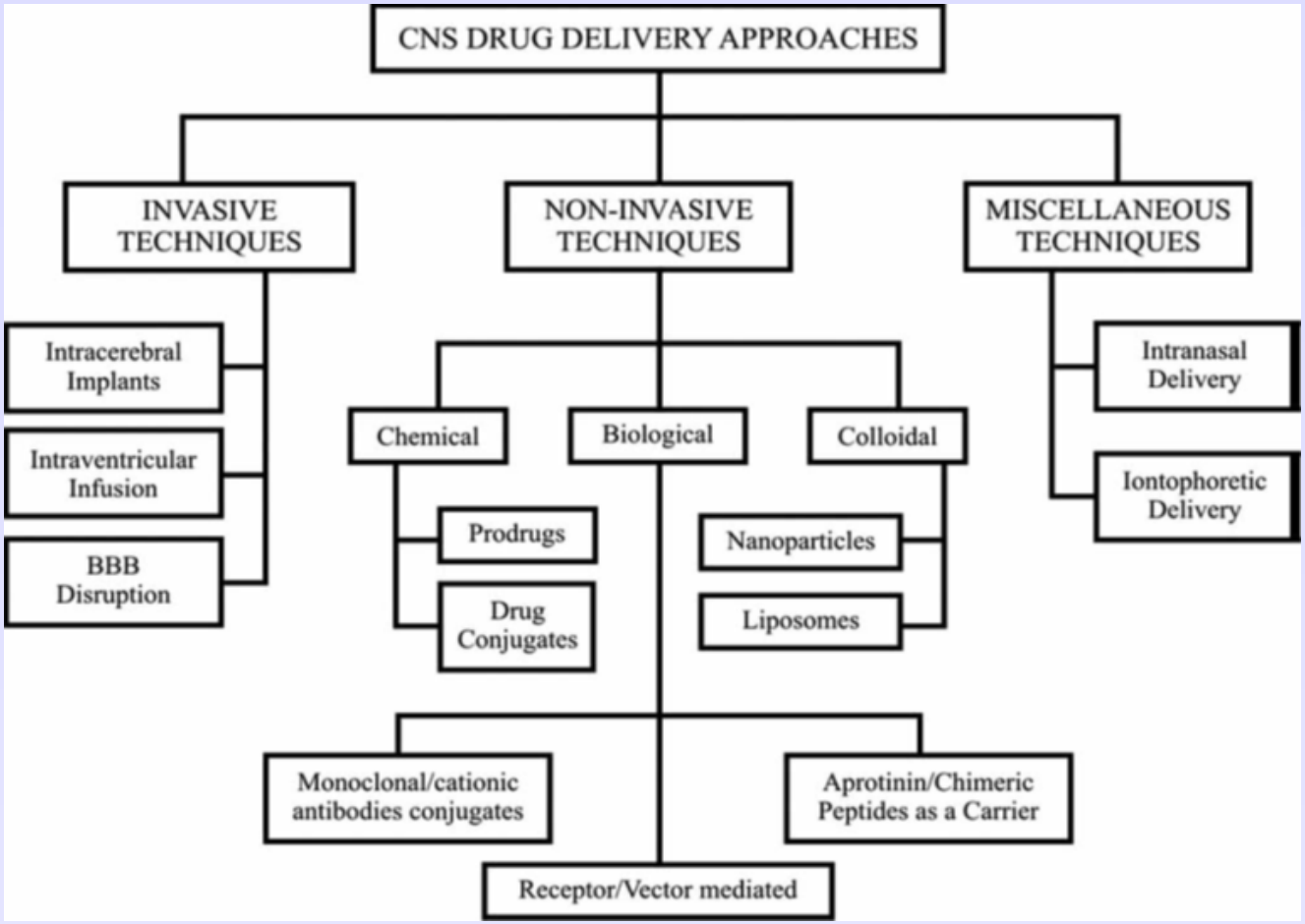


Fig. Strategies to enhance brain penetration of CNS therapeutics. (1) Opening of the BBB can be achieved by disintegrating the tight junctional complex. (2) Modulation of BBB efflux transporter function or inhibition of the induction of efflux transporters results in a more specific enhancement of brain penetration rates. (3) Use of nano-sized carrier systems and drug conjugates allows bypassing of BBB efflux transporter molecules. (4) Direct intracerebral administration (e.g., by implantation of release systems) bypasses the barriers and results in much higher local drug concentrations

Strategies to overcome difficulties with delivery of drugs to BBB



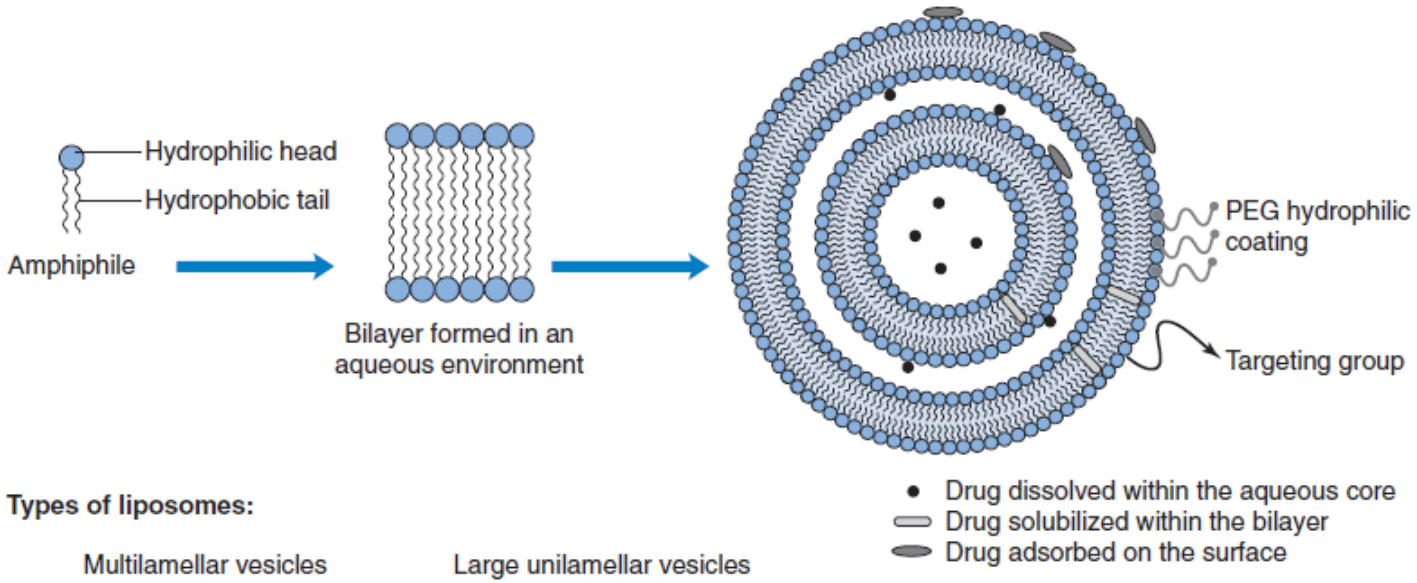
Nano-Sized Carrier Systems

Ideal Properties of Nano-Drug Delivery Systems for Drug Delivery Across the BloodBrain Barrier

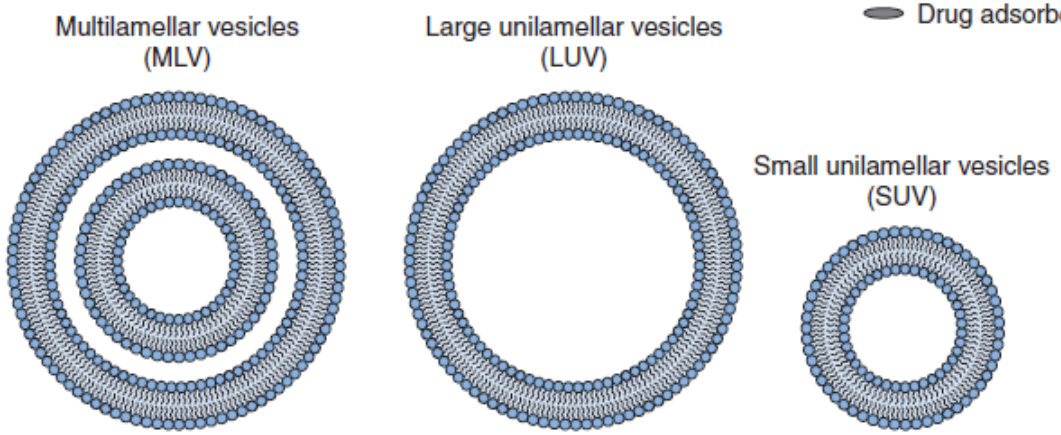
General for drug delivery
Nontoxic, biodegradable, and biocompatible
Amenable to small molecules, peptides, proteins, or nucleic acids (genes, antisense drugs)
Minimal nano-DDS excipient-induced drug alteration (chemical degradation/alteration, protein denaturation)
Modulation of drug-release profiles
Scalable and cost-effective manufacturing process
General for free circulation in blood
No capillary filtration: particle diameter <1 μm
Physical stability in blood (no aggregation, no dissolution, no interaction with blood cells)
Avoidance of the MPS, prolonged blood circulation time
Particular for brain delivery
Noninvasive delivery from the blood circulation into the brain parenchyma via the BBB without inducing BBB alteration, therefore by a transcytotic pathway
Particle diameter <100 nm to fit the loading capacity of transcytotic vesicles
Extra- or intracellular drug delivery to subset of brain cells or brain tumor cells

Abbreviations: BBB, blood–brain barrier; DDS, drug delivery system; MPS, mononuclear phagocyte system.

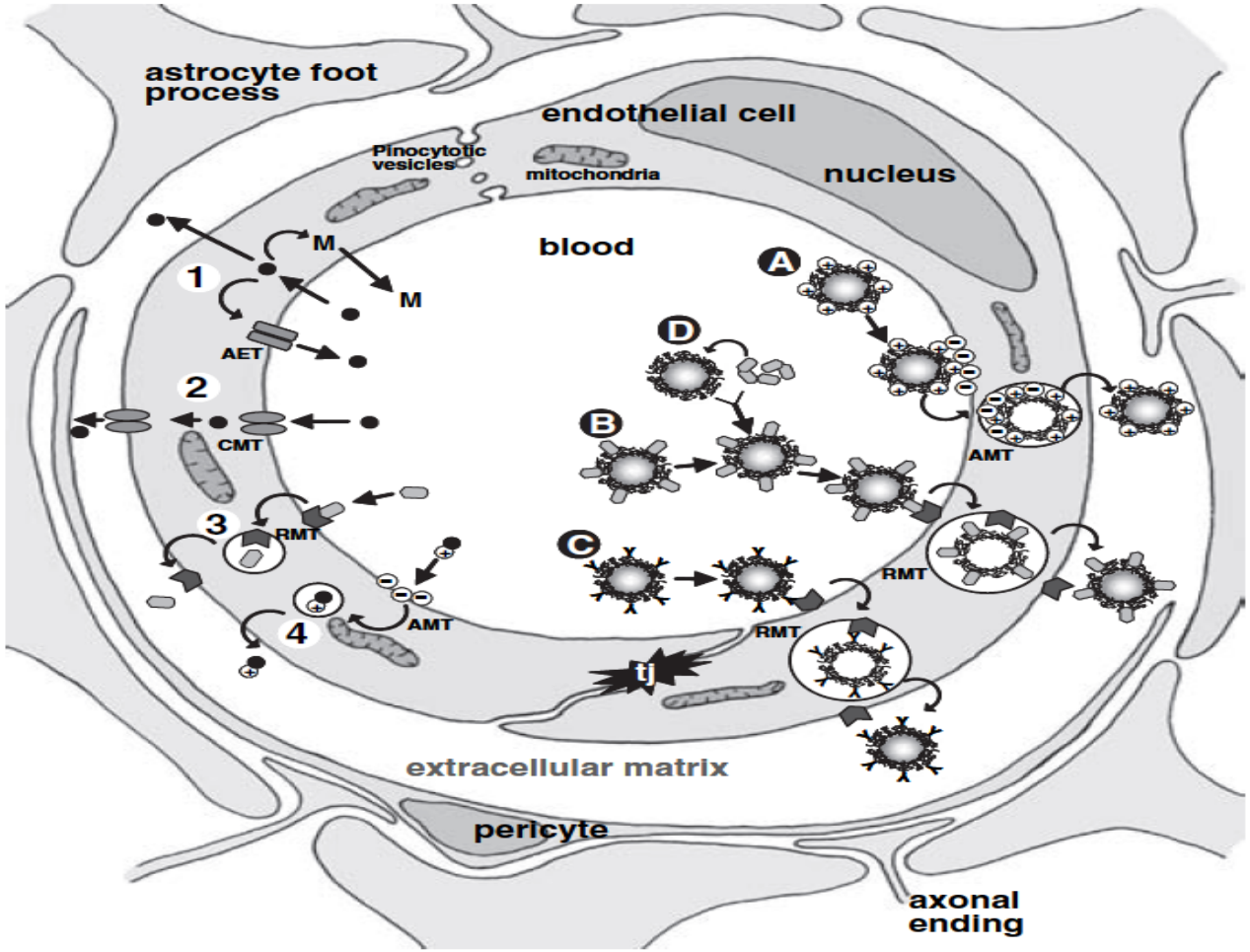
Liposomes is an example of Nanoparticles



Types of liposomes:



• A lipid, which can form bilayer vesicles with drug entrapped in the aqueous phase or the bilayer. The liposome surface can be modified with a PEG hydrophilic coating and targeting groups.



Schematic diagram of the neurovascular association forming the BBB together with the molecular transport pathways across the BBB (1–4) and proposed transcytotic brain-delivery mechanisms for nano-DDSs (A–D).AET, Active efflux transport; AMT, absorptive-mediate transcytosis; BBB, blood–brain barrier; CMT, carrier-mediated transport; DDSs, drug delivery systems; RMT, receptor-mediated transcytosis.

Intranasal Administration

Nasal drug administration is considered to provide one putative means for targeted CNS drug delivery. Three pathways are generally postulated for a drug administered to the nasal cavity to follow:

- Direct delivery to the brain, e.g., along nerve sheaths,

To what extent a molecule passes along these routes and to what extent it is thus indeed targeted to the CNS critically depends on its chemical features and its formulation.
It is currently rather questionable whether intranasal administration can be considered as a means for efficacious brain targeting.

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- Axonal transport along neurons
- Entry into the blood from the nasal mucosa

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Nasal Drug delivery to Body

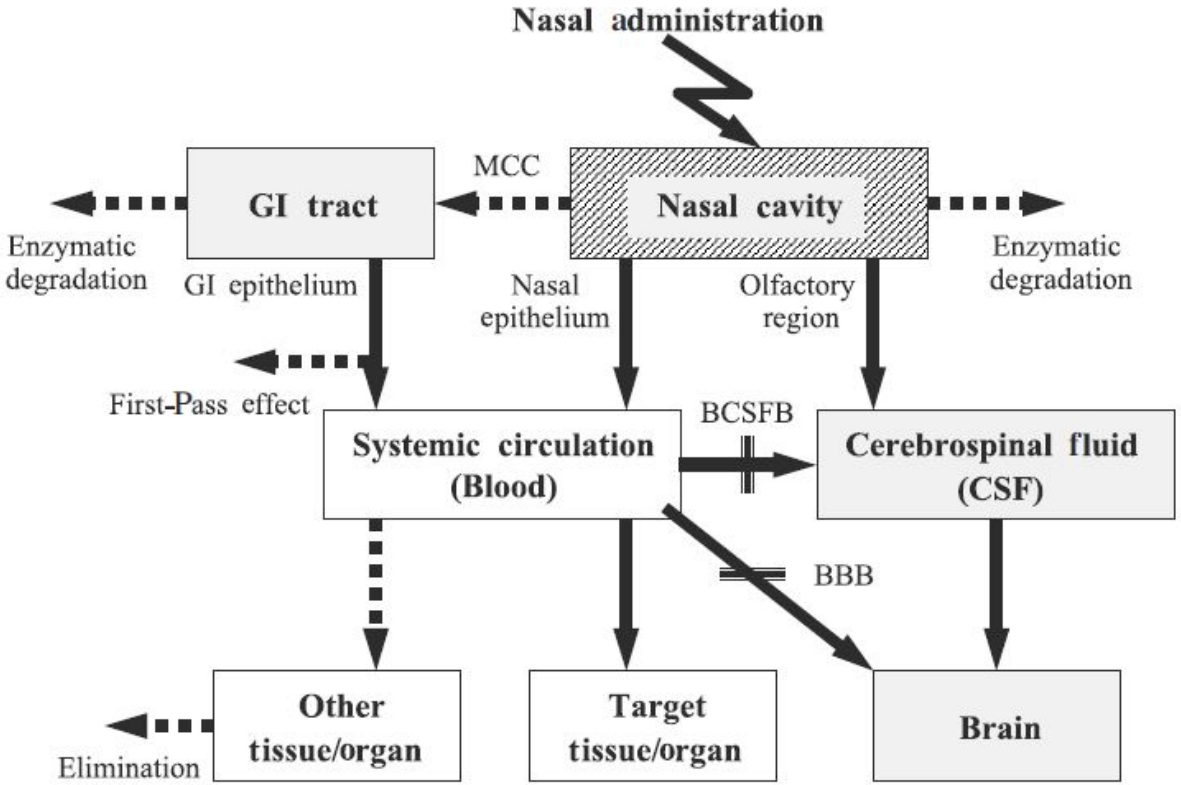

Fig. 8 Possible transportation routes of drugs after nasal administration. MCC = mucociliary clearance; BBB = blood–brain barrier; BCSFB = blood–CSF barrier.

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- Following delivery to the CSF, APIs still have to pass the ependymal brainCSF barrier. This is feasible for many small and lipophilic compounds.
- However, penetration into the parenchyma is limited due to tortuosity, transcapillary loss, cell uptake, and binding. Therefore, drugs administered to the CSF have minimal access to the parenchyma by diffusion

Implants

Implants are defined as sterile solid drug products made by compression, melting, or sintering. They generally consist of the drug and rate-controlling excipients

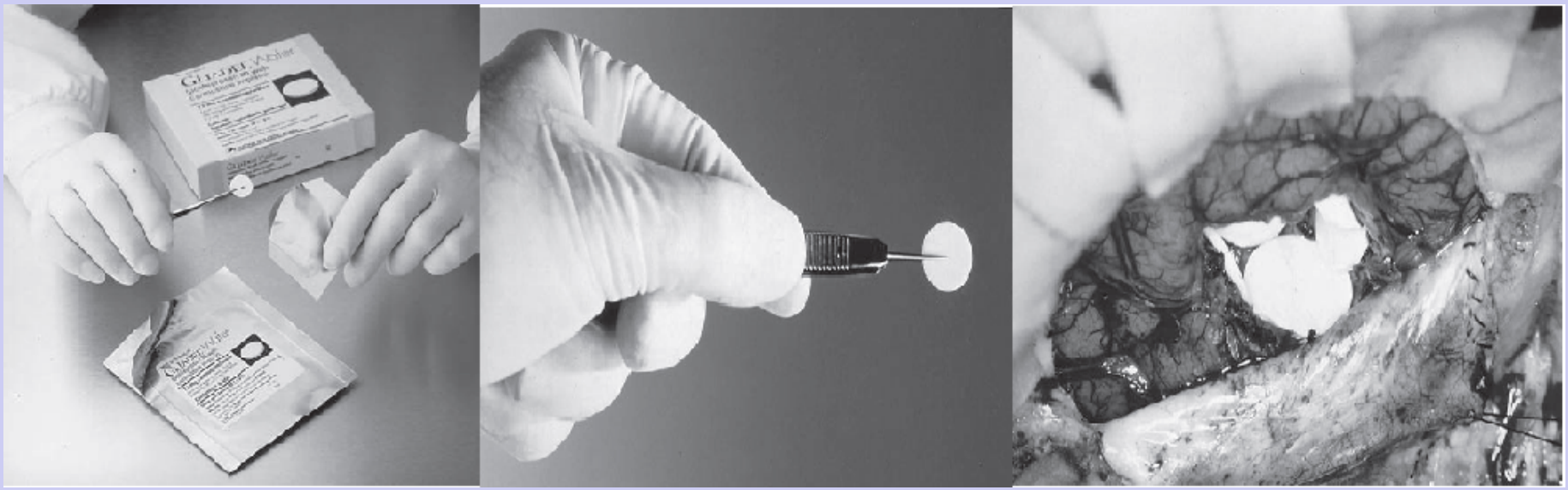
Implantable controlled release systems can be designed from both degradable and non-degradable polymers.Appropriately designed, polymers can provide reliable sustained release for periods of days to many years

A general drawback of controlled release systems for different indications is that the local penetration of the drug is limited due to the restriction of diffusion by the brain parenchyma

Implants

Controlled release systems are already used clinically for treatment of brain tumors.Intracranial implantation of a wafer loaded with carmustine (BCNU) following surgical debulking of the tumor was well tolerated in patients with malignant gliomas and resulted in a modest improvement of patient survival

Wafer: a thin slice of a material containing a medicinal agent.



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- Alternative approaches for direct delivery include gene therapy involving viral, lipid, polymer-based, and cell-based delivery strategies.

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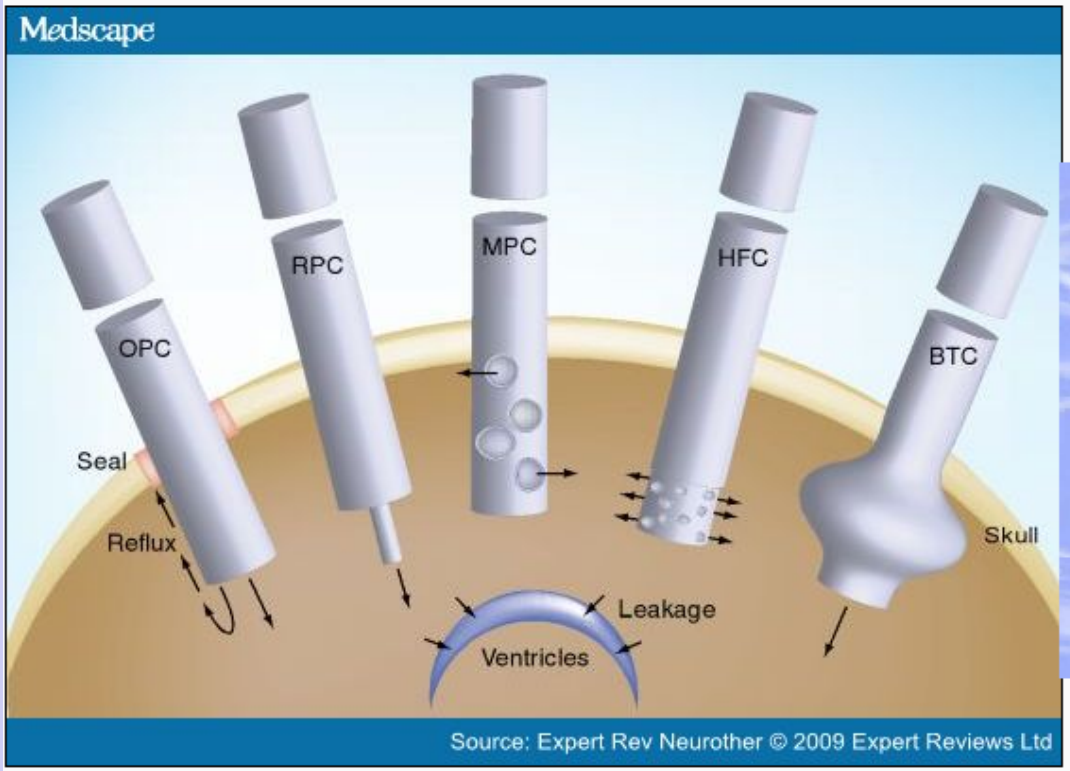

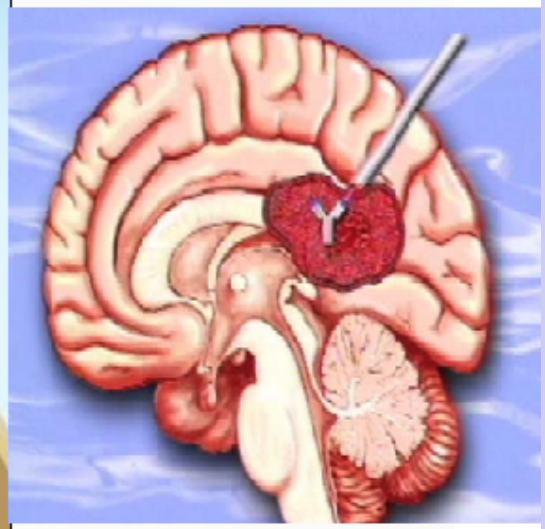

Figure

Schema of several catheters tested for convection-enhanced delivery. Arrows symbolize the flow of infusate during convection-enhanced delivery.

BTC: Balloon-tipped catheter; HFC: Hollow fiber catheter; MPC: Multiple port catheter; OPC: One port catheter; RPC: Reflux-preventing catheter.

Conclusions

Technology now exists for designing safe brain-targeted long-circulating nano- DDSs. The PEGylated immunoliposomes based on the concept of molecular Trojan horse that targets the transcytotic BBB receptors and ferries the liposomes though the BBB permitted the efficient noninvasive, nonviral delivery of plasmid genes into the brain parenchyma cells.

Conclusions

In recent years awareness of the impact of brain efflux transporters on treatment of CNS diseases has progressively increased

Further research. may provide new approaches which prevent a strengthening of BBB function in CNS diseases, and may thereby prevent development of pharmacoresistance.